

REMARKS

Applicant has carefully reviewed and considered the Office Action dated July 2, 2003 and the Advisory Action dated January 28, 2004. Applicant requests that the Amendment and Response mailed December 2, 2003 be entered. Thus, the pending claims are claims 1 and 3-9.

Interview Summary

Applicant thanks Examiner Winkler for the courtesies extended to Applicants' Representative during the telephone interview of May 28, 2004. Issues relating to the clarification of the experiments performed in 2003 as described in the Declarations dated March 28, 2003 and November 28, 2003 were discussed.

Rejection of the Claims under 35 U.S.C. Section 112, Second Paragraph

The examiner has maintained the rejection of Claims 1-9 under 35 U.S.C. Section 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. In particular, the examiner states that applicants' own disclosure in the specification on page 26, lines 10-13 states that the Dh-OLF isolated herein at fraction 27.5 showed and identical chromatographic retention to the standard component dho-B. Claim 2 has been cancelled. Insofar as this rejection is applied to the pending claims 1 and 3-9, it is hereby traversed.

It should be noted that page 26, lines 10-13 of the specification indicates that under the experimental conditions used for those experiments, Dh-OLF (a mammalian compound) and dho-B (a plant compound) have identical chromatographic retention times. As is well known in the art, if experimental conditions are modified, the results may change. Indeed, when the inventors made the experimental conditions more sensitive, the resolution of the HPLC columns was improved (See, Supplemental Declaration of Dr. Valdes dated June 2, 2004). Although the inventors used similar HPLC techniques in the experiments described on page 26 of the specification and in the experiments described in the Declaration of March 28, 2003 and November 28 2003 ("the later experiments"), several changes were made to the procedure that permitted detection of subtle differences in chromatographic migration between Dh-OLF and

dho-B. These differences in chromatographic migration can only be obtained if the structures of the mammalian compound (Dh-OLF) are different from the plant compound (dho-B).

First, in the later experiments, the inventors increased the sensitivity of detection by using a different antibody. In the experiments described in the specification, the antibody was raised against plant compounds, dho-A and dho-B (*i.e.*, would bind to dho-A, dho-B and Dh-OLF). In the later experiments, the antibody was raised against only dho-B (*i.e.*, would bind mainly to dho-B and Dh-OLF, and much less so to dho-A). This increased antibody specificity allowed the inventors to inject smaller quantities of Dh-OLF and dihydroouabain into the HPLC columns.

Second, in the later experiments, the inventors collected smaller elution fractions from the HPLC column [30 sec (0.5 mL) collection in the later experiments, instead of 60 sec (1 mL) in the experiments described in the specification]. Smaller collection volumes allows for detection of increased resolution in the separation. Thus, the inventors detected two distinct peaks separated by a minimum of one minute (Figure 2 of November 28, 2003 Declaration), instead of one more-diffuse peak detected previously.

Third, in order to further clarify that Dh-OLF (mammalian compound) was different from dho-B (plant compound), the two compounds were deglycosylation by acid hydrolysis to produce the genin-species. Because the genin-species are smaller, finer resolution of chemical structures is possible. When the inventors measured the HPLC mobility of the individual genin-species (Dh-OLF-genin and dho-B-genin), they eluted at 18 and 20 minutes respectively (see Figure 3 attached to Declaration dated November 28, 2003). Thus, the respective genins migrate differently for the two compounds. Therefore, they must have fundamentally different structures.

It is also important to note that during the first experiments (*i.e.*, those described in the specification) the inventors never chromatographed the compounds together (mixed). In the later experiments, the four compounds (Dh-OLF, dho, Dh-OLF-genin, and dho-genin) were all run simultaneously in the same column, and generated four distinct peaks (See Figure attached to March 28, 2003 Declaration and Figure 3 attached to November 28, 2003 Declaration). Thus, subtle differences due to small variability between HPLC runs rather than to differences in structure are completely eliminated. This provides convincing evidence that Dh-OLF (a

compound isolated from mammals) is structurally different than dihydroouabain-B (a compound isolated from plants).

It should be further noted that it is well known in the art that the reverse phase C-18 HPLC chromatography used by the inventors separates compounds based primarily on their polarity and solubility properties. Thus, it is well established that many different compounds can migrate under one HPLC peak and have different structures, but have similar polarities and solubilities. The reverse, however, is definitive in that, if compounds separate, they must be different in structure, otherwise they would not have different polarities or solubilities.

The pending claims recite a "purified mammalian dihydroouabain-like factor (Dh-OLF)." As indicated above, Dh-OLF structurally is a different compound from dho (either dho-A or dho-B) and therefore distinctly claims the subject matter that applicant regards as the invention. Thus, applicant request that the rejection of claims 1 and 3-9 under 35 U.S.C. Section 112, second paragraph be withdrawn.

Rejection of the Claims under 35 U.S.C. Section 102(b)

Claims 1-9 were rejected under 35 U.S.C. Section 102(b) as being anticipated by Klaus Repenning (US 3,113,128). Also claims 1-9 were rejected under 35 U.S.C. Section 102(b) as being anticipated by Qazzaz et la. (Abstract FASEB Journal 1997). Claim 2 has been cancelled. Insofar as these rejection s are applied to the pending claims 1 and 3-9, they are hereby traversed.

In particular, the Examiner indicates that dho-B from a plant source is the same as the Dh-OLF derived from a mammalian source. As discussed in detail above, under certain experimental conditions Dh-OLF and dho-B have similar chromatographic retention values, but that under more sensitive experimental conditions, Dh-OLF and dho-B, in fact, have different chromatographic retention values, indicating that Dh-OLF (a mammalian compound) and dho-B (a plant compound) are indeed different compounds. Thus, the compounds as recited by the present claims are distinguishable over the cited art.

Applicant request that the rejections of claims 1 and 3-9 under 35 U.S.C. Section 102(b) be withdrawn.

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Conclusion

Applicants respectfully submit that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (612)-337-2540 to facilitate prosecution of this application.

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Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.



Date: 2 June 2004

Respectfully submitted,

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